REMARKS

Reconsideration and allowance in view of foregoing amendments and the following remarks are respectfully requested. Claims 1, 4, 5, 12, 15 and 16 are presently pending in this application and stand rejected.

By this Amendment, independent claims 1 and 12 have been amended. More specifically, each claim has been amended to specifically recite that the stable cell lines are "adhesion" cell lines of mammalian neural precursor cells prepared from an "adhesion" culture of neural precursor cells.

Support for these amendments can be found, for example, on page 12, line 10 to page 15, line 5, as well as throughout the specification. Page 12, lines 11-13, specifically states that the stem cells were prepared according to previously reported procedure (U.S. Patent 5,753,506) and "plated." On page 13, lines 7-9 and lines 19-20, the cells were "replated." On page 15, line 2, the cells were differentiated by "plating." Plating requires adhesion cultures. Only adhesion cultures can be plated; suspension cultures, by definition, are not plated. Thus, all examples on pages 12-15 of the present application and all examples in U.S. Patent 5,753,506 (Johe) are of

adhesion cultures. Furthermore, the present application claims priority to U.S. Patent 5,753,506 (Johe) which is incorporated by reference in its entirety. Thus, no new matter has been added by these amendments.

Rejections Under 35 USC 112, First Paragraph

On pages 2-3, in numbered paragraph 4, of the Official Action, the Examiner rejects claims 1, 4-5, 12 and 15-16 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner states that no proper antecedent basis or conception exists for the broader concept of neural precursor cells maintaining normal karyotypes and normal neuronal phenotypes beyond thirty cell doublings.

In an effort to advance the prosecution of this application and without acceding to the position of the Examiner, Applicants have amended independent claims 1 and 12 by deleting reference to the cell lines maintaining normal karyotypes and normal neuronal phenotypes beyond thirty cell doublings.

In view of these amendments, it is respectfully requested that this rejection be withdrawn and that claims 1, 4-5, 12 and 15-16, as amended, be allowed.

Claim Rejections - 35 USC § 103

On pages 3-6, in numbered paragraph 5, of the Official Action, the Examiner maintains the rejection of claims 1, 4-5, 12 and 15-16 under 35 USC 103(a) as being unpatentable over Nakafuka et al. (J. Neuroscience Res. 41:153-168, 1995) in view of Weiss et al. (U.S. Patent 5,851,832). In this rejection, it is the position of the Examiner that claims 1, 4-5, 12 and 15-16 are obvious over the combination of the teachings of the cited references.

On pages 6-7, in numbered paragraph 6, of the Official Action, the Examiner maintains the rejection of claims 1, 4-5, 12 and 15-16 under 35 USC 103(a) as being unpatentable over Nakafuka et al. (J. Neuroscience Res. 41: 153-168, 1995) in view of Weiss et al. (U.S. Patent 5,851,832) and further in view of Eilers et al. (Nature 340: 66-68, 1989) and/or Evans et al. (Science 240: 889-895, 1988). In this rejection, it is the position of the Examiner that claims 1, 4-5, 12 and 15-16 are obvious over the combination of the teachings of the cited references.

These rejections are respectfully traversed. First, Applicants have amended each of independent claims 1 and 12 to specifically recite that the stable cell lines of the present invention are "adhesion" cell lines of mammalian neural precursor cells prepared from an "adhesion" culture of neural precursor cells.

Second, Nakafuku et al. teaches use of serum to initiate an adhesion culture of neuroepithelial precursor cells, which is then infected with the mycer construct to derive cell lines. The cell lines thus derived, however, exhibit a very low level of neuronal differentiation (TABLE 1, page 162). The Examiner correctly surmises that the use of serum by Nakafuku et al. may have contributed to instability of the cell differentiation property. The adverse effect of serum on multipotential neural stem cells is also taught in the present invention.

The Examiner, however, asserts that, by starting from a serum-free culture of neural stem cells as taught by Weiss et al. and then combining the immortalizing method of Nakafuku et al., one can derive the present invention. The serum-free culture of Weiss et al., however, uses a "suspension" culture in which neural stem cells are cultured in bacterial petri dishes to promote aggregation

of the cells floating in the medium. The ability of the cells to form such suspended cell aggregates is taught by Weiss et al. to be a key innate property of neural stem cells and that the close cell-cell interaction occurring within such an aggregate is believed to be essential for the cells differentiation into neurons and glia.

In contrast, the present application teaches the propagation of neural stem cells as an "adhesion" culture. As noted above, the present application claims priority to U.S. Patent 5,753,506 (Johe) which is incorporated by reference in its entirety. A recent Ex Parte Reexamination Request of U.S. Patent 5,753,506 (Reexam Control Number 90/006,459) was denied on the grounds that U.S. Patent 5,851,832 (Weiss et al.) did not teach or disclose the "adhesion" neural stem cell cultures of U.S. Patent 5,753,506 (Johe).

More specifically, on pages 3-5 of the Request for *Ex Parte* Reexamination Pursuant to 37 CFR 1.510, Applicant stated:

> Since U.S. Patent 5,750,376 (Weiss et al.) and U.S. Patent 5,851,832 (Weiss et al.) have nearly identical specifications, reference to the specification will be limited to that for U.S. Patent 5,750,376 (Weiss et al.).
>
> A partial facsimile of claim 6 of U.S. Patent 5,753,506 (Johe) may be piecemeal reconstructed from

the specification of U.S. Patent 5,750,376 (Weiss et al.) as follows.

In column 11, lines 1-4, column 12, lines 15-24 and column 16, lines 14-15, U.S. Patent 5,750,376 (Weiss et al.) disclose neural stem cells adhered to a fixed substrate.

In column 12, lines 15-20, column 13, lines 5-6 and in Figure 1, U.S. Patent 5,750,376 (Weiss et al.) discloses the ability of cultured stem cells to maintain the multipotential capacity to differentiate into neurons, astrocytes, and oligodendrocytes.

In column 16, lines 36-39 and 53-54, column 18, lines 6-9 and in Example 3, U.S. Patent 5,750,376 (Weiss et al.) discloses the ability of cultured stem cells to divide in serum-free medium supplemented with a mitogen.

In column 18, lines 63-66 and in Example 7, U.S. Patent 5,750,376 (Weiss et al.) discloses the ability of cultured stem cells to differentiate upon withdrawal of mitogen.

However, U.S. Patent 5,750,376 (Weiss et al.) does not specifically disclose the in vitro adhesion culture of stem cells of claim 6 of U.S. Patent 5,753,506 (Johe). Claim 6 of U.S. Patent 5,753,506 (Johe) can only be piecemeal reconstructed from the specification of U.S. Patent 5,750,376 (Weiss et al.). Furthermore, the piecemeal reconstruction is incomplete because U.S. Patent 5,750,376 (Weiss et al.) only discloses suspension cultures of stem cells that maintain the multipotential capacity to differentiate into neurons, astrocytes, and oligodendrocytes; divide in serum-free medium supplemented with a mitogen; and differentiate upon withdrawal of mitogen.

At no point does U.S. Patent 5,750,376 (Weiss et al.) disclose adhesion cultures of stem cells that maintain the multipotential capacity to differentiate into neurons, astrocytes, and oligodendrocytes; divide in serum-free medium supplemented with a mitogen; and differentiate upon withdrawal of mitogen.

Thus, combining the teachings of the serum-free "suspension" culture of Weiss et al. using bFGF and/or EGF

and the myc-er construct plus serum of Nakafuku et al. is expected to produce a "suspension" culture of neural stem cells, but not the "adhesion" culture of neural stem cells disclosed in the present invention.

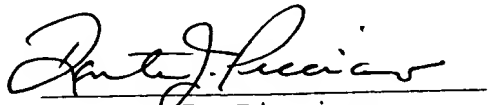
In view of the amendments to claims 1 and 12 and the above-given explanation, it is respectfully submitted that no combination of the teachings of the cited references would result in stable "adhesion" cell lines. It is, therefore, respectfully requested that these rejections be withdrawn and that claims 1, 4-5, 12 and 15-16 be allowed.

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited.

Should any matters remain in this application which might be resolved by interview, the Examiner is requested to telephone the undersigned at (570) 386-5744.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

By: 

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